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EDITORIAL COMMENT

A Dose Response for Cardiac Resynchronization Therapy?*

Mitchell N. Faddis, MD, PhD, FACC

St. Louis, Missouri

The consequence of synchronous, rapid activation of the left ventricle (LV) by the cardiac conduction system is an efficient economy of energy expenditure for the work of ejection during the cardiac cycle. In the failing heart with concomitant conduction system disease, this economy is disrupted, resulting in several detrimental effects to cardiac function. First, a significant portion of energy expended in the cardiac cycle does not contribute to external cardiac work. Instead, dyssynchronous contraction of the septum and lateral wall allow for energy to be wasted on motion of the partially relaxed opposite wall rather than on the work of blood ejection (1). Second, the isovolumetric phases of the cardiac cycle are expanded relative to systolic ejection and diastolic filling periods, increasing "wasted time" (2). Third, the lateral wall is subjected to an excessively high wall strain, in the case of left bundle branch block, with resulting molecular changes that contribute to myopathic changes (3). The result of this pathophysiology is a worse prognosis than heart failure uncomplicated by conduction system disease (4).

See page 355

Biventricular pacing was first proposed as a way to restore, to some degree, electrical synchronization of the septum and lateral wall of the LV in the setting of left bundle branch block. In the first description of a series of patients with refractory heart failure and conduction system disease, biventricular pacing produced substantial clinical improvements in most, but not all, patients (5). Subsequent randomized clinical trials have consistently verified these clinical benefits as well as providing evidence for a modification of the natural history of severe heart failure in patients treated with a "state-of-the-art" heart failure medical regimen manifested by a reduction in mortality and incidence of heart failure decompensation (6,7).

As a result, cardiac resynchronization therapy (CRT) has become a standard of care for the treatment of patients with LV conduction delay and concomitant systolic heart failure that has become unresponsive to medical therapy. Despite a consensus on the clinical benefits of CRT, many questions remain regarding the optimal implementation of this revolutionary therapy and a nonresponder rate in the range of 30%.

In this issue of the *Journal,* Koplan et al. (8) examine whether the percentage of all heart beats that are biventricularly paced contributes to the magnitude of the observed reduction in the combined end point of heart failure hospitalization and all-cause mortality resulting from CRT. A post-hoc analysis is applied to data collected from 1,812 patients derived from 2 large registries containing patients with CRT devices. In both registries, follow-up data were collected at 3-month intervals for 1 year after implant. The authors divided the patient cohort into quartiles based upon lifetime percent biventricular pacing. A Kaplan-Meier survival analysis was then performed with regard to freedom from heart failure hospitalization and all-cause mortality.

The authors observed that, in the top 3 quartiles, in which patients paced more than 92% of the time, there was a 44% reduction in risk of events compared with the bottom quartile, which comprised of patients with biventricular pacing 0% to 92%. In addition, patients who received biventricular pacing 100% of the time, or the top quartile, had significantly better outcomes than all of the other quartiles. The clinical nonresponse rate was slightly lower in the >92% pacing, 54% versus 46%, but percent biventricular pacing could not explain the entire nonresponse rate.

The authors observed several mechanisms for a reduction in biventricular pacing. The most intuitively obvious was a loss of LV lead function due to dislodgement or lack of capture in 6.6% of patients in the bottom quartile. Atrial arrhythmias also contributed significantly to a reduction in biventricular pacing percentage, presumably resulting from periods of intrinsic conduction above the programmed lower rate limit. A related characteristic observed in the lowest quartile was a relative underutilization of the ventricular rate regulation feature, whereby biventricular pacing in the presence of atrial fibrillation is increased by dynamic adjustment of the lower rate limit. A third mechanism that may have contributed to a reduction in biventricular pacing percentage was intrinsic conduction "beating" the programmed atrioventricular (AV) delay. This possibility is supported by a significantly longer programmed AV delay in the bottom quartile.

Is there a dose-response for CRT? You cannot say from these data. The intention of treatment in all patients was to achieve 100% biventricular pacing. Interestingly, this was only realized in the top quartile of patients, although 75% had more than 92% biventricular pacing. The lowest quartile appears to be inhomogeneous in regard to percent biventricular pacing. A significant number had no biven-

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From Washington University, St. Louis, Missouri. Dr. Faddis is a consultant for Boston Scientific Corporation and St. Jude Medical Corporation.

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tricular pacing because the LV lead had been turned off. In the remainder, LV pacing was active most of the time. The marked reduction in benefit in this quartile suggests an essentially all or none effect of biventricular pacing. In patients with significant biventricular pacing percentages in the lowest quartile, it is possible that insufficient LV pre-excitation occurred to allow for significant resynchronization of the left ventricle. Additional information that would have shed further light on this possibility is measurement of the intracardiac atrial sense or pace to LV sense interval. Other mechanisms of ineffective CRT such as inappropriate lead location may also have been operative but this seems unlikely to be concentrated in the lowest quartile.

What about atrial fibrillation? Although, atrial fibrillation was more likely in the lowest quartile, other information suggests that heart failure patients with atrial fibrillation can respond to CRT to a similar degree as patients in normal sinus rhythm (9). The added challenge to provide clinical benefits of CRT in atrial fibrillation patients is to ensure biventricular pacing through adequate blockade of native conduction through the AV node. When this is not possible pharmacologically, catheter ablation of the AV node has been shown to be useful to enhance the efficacy of CRT (10). The ventricular rate regulation feature, which was not used as much in the lowest quartile patients of this study, provides a means of dynamic adjustment of the lower rate limit as an additional means to ensure adequate biventricular pacing.

In summary, what should the target be for biventricular pacing percentage? This analysis suggests that benefits of CRT require pacing percentages as close to 100% as possible. Beyond simple pacing percentages, however, there appears to be additional opportunities to improve the clinical response to CRT that continues to be plagued by a significant nonresponse rate. Whether advancement of LV pre-excitation through V-V interval adjustment may increase the clinical response to CRT was not tested in this study. Additional methods of visualizing the adequacy of LV resynchronization and guiding atrioventricular delay and V-V delay programming through tissue Doppler echocardiography (11) or electrocardiographic imaging (12) may provide the opportunity to further improve CRT delivery. Guidance of the LV lead implantation site to areas of the LV predicted by pre-operative imaging may also provide an additional tool to improve the delivery of adequate resynchronization.

Reprint requests and correspondence: Dr. Mitchell N. Faddis, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8086, St. Louis, Missouri 63110. E-mail: mfaddis@wustl.edu.

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